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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/488,867	01/21/2000	Michael J. Imperiale	11203-002001	5039

20985 7590 11/27/2001

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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 11/27/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/488,867	Applicant(s) IMPERIALE, MICHAEL J.	
	Examiner Brian Whiteman	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Claims 1-39 are pending in this pending application.

Claim Objections

Claim 9 is objected to because of the following informalities: The wording of the phrase on page 38, line 11 should read, "fiber gene, hexon gene, or combination thereof." Appropriate correction is required.

Claim 33 is objected to because of the following informalities: The wording of the phrase on lines 25-26 should read, "transforming two adenovirus replication defective sequences into an adenovirus replication competent host cell, wherein the two sequences comprise." Appropriate correction is required.

Claim Rejections - 35 USC § 112

In light of the claims and compact prosecution, rejections under 112, second paragraph are required first in order to understand any rejections under 112, first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-20, 27-33, and 35-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-16, 20, and 36-39 are vague and indefinite as to what is intended to be encompass with regard to a nucleic acid sequence encoding a polypeptide having the first activity of a first adenovirus serotype trans-acting protein and lacking the activity of a second

adenovirus serotype trans-acting protein. The disclosure does not define the metes and bounds of the phrase. It is not apparent in view of the disclosure how a sequence can have the activity of a first adenovirus serotype trans-acting protein and lacking the activity of a second adenovirus serotype trans-acting protein. In addition, the claims do not define how the phrase is operatively linked as a vector system in order to package the replication defective adenovirus nucleic acid sequences of claim 1. In light of the disclosure and compact prosecution, the claims read on a vector system either comprising 1) a nucleic sequence comprising 5' and 3' adenovirus ITRs, an adenovirus serotype cis-acting packaging signal, a heterologous nucleic acid; a helper virus comprising: 5' and 3' adenovirus ITRs, a nucleic acid sequence comprising an adenovirus serotype cis-acting packaging sequence and a functional 52/55 kDa trans-acting protein; or 2) a nucleic sequence comprising 5' and 3' adenovirus ITRs, an adenovirus serotype cis-acting packaging signal sequence, a heterologous nucleic acid, and a mutated adenovirus serotype 52/55 kDa trans-acting protein that is not functional; and introducing the nucleic acid sequence into a cell, which is genetically modified to express a functional adenovirus serotype 52/55 kDa trans-acting protein. If the claims are intended to encompass these two statements listed above, then the applicant should re-write the claims to read on these statements.

The term "hexon polypeptide gene" in claim 9 is a relative term, which renders the claim indefinite. The term "hexon polypeptide gene" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The disclosure does not define the metes and bounds of the phrase. It is apparent how a hexon protein can be a polypeptide and a gene at the same time. Clarification is requested.

Claim 10 is vague and indefinite as to what is intended to be encompass with regard to a the vector system of claim 1, wherein the inability to produce a functional 52/55 kDa trans-acting protein is due to a mutation in the sequence encoding the protein. The disclosure does not define the metes and bounds of the claim. It is not apparent in view of the disclosure which sequence claim 10 is referring to in claim 1 and claim 10 does not define how the inability to produce a functional 52/55 kDa trans-acting protein is operatively linked as a vector system in order to package the replication defective adenovirus nucleic acid sequences of claim 1.

Claims 13, 14, and 28 are vague and indefinite as to what is intended to be encompass with regard to the vector system of claim 1 or the kit of claim 27, wherein the nucleic acid sequence further comprising an adenovirus replication competent host cell. The disclosure does not define the metes and bounds of the claim. It is not apparent how a nucleic acid sequence can further comprise an adenovirus replication competent host cell. Clarification is requested.

Claim 17 is incomplete and renders the claim vague and indefinite. It is unclear as to what is intended to be encompass be encompass with regard to a nucleic acid sequence encoding a polypeptide having the first activity of a first adenovirus serotype 52/55 kDa trans-acting protein and lacking the ability to produce a polypeptide having the activity of a second adenovirus serotype 52/55 kDa trans-acting protein. The disclosure does not define the metes and bounds of the phrase. It is not apparent in view of the disclosure how a sequence can have the activity of a first adenovirus serotype 52/55 kDa trans-acting protein, lacking the activity of a second adenovirus serotype 52/55 kDa trans-acting protein, when the claims do not define how the phrase is operatively linked as a vector system in order to package the replication defective adenovirus nucleic acid sequences of claim 17.

Claim 18 is incomplete and renders the claim vague and indefinite. It is unclear as to what is intended to be encompass be encompass with regard to a cell comprising a nucleic acid sequence encoding a polypeptide having the first activity of a first adenovirus serotype 52/55 kDa trans-acting protein. The disclosure does not define the metes and bounds of the phrase. It is not apparent in view of the disclosure how a sequence can have the activity of a first adenovirus serotype trans-acting protein, when the claim does not define how the phrase operatively linked as a vector system in order to package the replication defective adenovirus nucleic acid sequences of claim 18.

Claim 19 is incomplete and renders the claim vague and indefinite. It is unclear as to what is intended to be encompass with regard to an expression cassette comprising a nucleic acid sequence encoding a polypeptide having the first activity of a first adenovirus serotype 52/55 kDa trans-acting protein. The disclosure does not define the metes and bounds of the phrase. It is not apparent in view of the disclosure how a sequence can have the activity of a first adenovirus serotype trans-acting protein, when the claim does not define how the phrase operatively linked as a vector system in order to package the replication defective adenovirus nucleic acid sequences of claim 19.

Claim 27 is incomplete and renders the claim vague and indefinite. It is unclear as to what is intended to be encompass with regard to a nucleic acid sequence encoding a polypeptide having the first activity of a first adenovirus serotype 52/55 kDa trans-acting protein. The disclosure does not define the metes and bounds of the phrase. It is not apparent in view of the disclosure how a sequence can have the activity of a first adenovirus serotype trans-acting

protein, when the claim does not define how the phrase operatively linked as a vector system in order to package the replication defective adenovirus nucleic acid sequences of claim 27.

Claim 29 is incomplete and renders the claim vague and indefinite. It is unclear as to what is intended to be encompass with regard to the kit of claim 27, wherein the nucleic acid sequence further comprising an expression cassette. The disclosure does not define the metes and bounds of the claim. It is not apparent how a nucleic acid sequence can further comprise an expression cassette. Clarification is requested.

Claim 30 is incomplete and renders the claim vague and indefinite. It is unclear as to what is intended to be encompass with regard to the kit of claim 27, wherein the second replication defective adenovirus sequence further comprises the nucleic acid sequence encoding a polypeptide having the activity of a first adenovirus serotype 52/55 kDa trans-acting protein. The disclosure does not define the metes and bounds of the phrase. It is not apparent in view of the disclosure how a sequence can have the activity of a first adenovirus serotype trans-acting protein, when the claim already has a nucleic acid sequence encoding a polypeptide having the activity of a first adenovirus serotype 52/55 kDa trans-acting protein. In addition, the claim does not define how the phrase operatively linked as a vector system in order to package the replication defective adenovirus nucleic acid sequences of claim 30.

Claim 31 is incomplete and renders the claim vague and indefinite. It is unclear as to what is intended to be encompass with regard to a nucleic acid sequence encoding a polypeptide having the activity of a first adenovirus serotype 52/55 kDa trans-acting protein. The disclosure does not define the metes and bounds of the phrase. It is not apparent in view of the disclosure how a sequence can have the activity of a first adenovirus serotype trans-acting protein, when the

claim does not define how the phrase operatively linked as a vector system in order to package the replication defective adenovirus nucleic acid sequences of claim 31.

Claim 32 is incomplete and renders the claim vague and indefinite. It is unclear as to what is intended to be encompass with regard to a nucleic acid sequence encoding a polypeptide having the activity of a first adenovirus serotype 52/55 kDa trans-acting protein. The disclosure does not define the metes and bounds of the phrase. It is not apparent in view of the disclosure how a sequence can have the activity of a first adenovirus serotype trans-acting protein, when the claim does not define how the phrase operatively linked as a vector system in order to package the replication defective adenovirus nucleic acid sequences of claim 32.

Claim 33 is incomplete and renders the claim vague and indefinite. It is unclear as to what is intended to be encompass with regard to a nucleic acid sequence encoding a polypeptide having the activity of a first adenovirus serotype 52/55 kDa trans-acting protein. The disclosure does not define the metes and bounds of the phrase. It is not apparent in view of the disclosure how a sequence can have the activity of a first adenovirus serotype trans-acting protein, when the claim does not define how the phrase operatively linked as a vector system in order to package the replication defective adenovirus nucleic acid sequences of claim 33.

Claim 35 is incomplete and renders the claim vague and indefinite. It is unclear as to what is intended to be encompass with regard to the phrase, "lacking the ability to produce a polypeptide having the activity of an adenovirus 7 serotype 52/55 kDa trans-acting protein." The disclosure does not define the metes and bounds of the phrase. It is not apparent in view of the disclosure how the phrase is operatively linked as a vector system in order to package the replication defective adenovirus nucleic acid sequences of claim 35.

In view of the disclosure and compact prosecution, the following 112 rejections, under first paragraph will be based on claims encompassing a vector system for selectively packaging a replication defective adenovirus nucleic acid sequence in an adenovirus capsid based on adenovirus serotype, comprising either: 1) A vector system for selectively packaging a replication defective adenovirus nucleic acid sequence in an adenovirus capsid based on adenovirus serotype, comprising a first nucleic sequence comprising 5' and 3' adenovirus ITRs, an adenovirus serotype cis-acting packaging signal, a heterologous nucleic acid; and a helper virus comprising: 5' and 3' adenovirus ITRs, a second nucleic acid sequence comprising an adenovirus serotype cis-acting packaging sequence and a DNA sequence encoding a functional 52/55 kDa trans-acting protein; wherein the adenovirus serotype of the first nucleic acid sequence is different then adenovirus serotype in the second nucleic acid sequence; 2) A vector system for selectively packaging a replication defective adenovirus nucleic acid sequence in an adenovirus capsid based on adenovirus serotype, comprising a first nucleic sequence comprising 5' and 3' adenovirus ITRs, an adenovirus serotype cis-acting packaging signal sequence, a heterologous nucleic acid, and a DNA sequence encoding a mutated adenovirus serotype 52/55 kDa trans-acting protein that is not functional; and a cell, which is genetically modified by transfecting the cell with a second nucleic acid sequence encoding a functional adenovirus serotype 52/55 kDa trans-acting protein, wherein the adenovirus serotype in the first nucleic acid sequence is different then adenovirus serotype in the second nucleic acid sequence.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-39 as best understood, are readable on a genus of a nucleic acid sequence encoding a polypeptide having the activity of a first adenovirus serotype 52/55 kDa trans-acting protein and lacking the ability of a second adenovirus serotype 52/55 kDa trans-acting protein, wherein the genus of nucleic acid sequences is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates production of a genus of a nucleic acid sequence encoding a polypeptide having the activity of a first adenovirus serotype 52/55 kDa trans-acting protein and lacking the ability of a second adenovirus serotype 52/55 kDa trans-acting protein. The as-filed specification provides sufficient description of a mutant adenovirus (H5pm8001) incapable of expressing the 52/55 kDa protein. The adenovirus comprises a nucleic acid sequence, which is mutated and is lacking the activity of an adenovirus serotype 5, 52/55 kDa trans-acting protein.

However, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of a nucleic acid sequence encoding a polypeptide having the activity of a first adenovirus serotype 52/55 kDa trans-acting protein and lacking the ability of a second adenovirus serotype 52/55 kDa trans-acting protein as claimed; what is required is the

knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of a nucleic acid sequence encoding a polypeptide having the activity of a first adenovirus serotype 52/55 kDa trans-acting protein and lacking the ability of a second adenovirus serotype 52/55 kDa trans-acting protein, and/or final products of a vector system that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed to a genus of a genus of a nucleic acid sequence encoding a polypeptide having the activity of a first adenovirus serotype 52/55 kDa trans-acting protein and lacking the ability of a second adenovirus serotype 52/55 kDa trans-acting protein. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming an unspecified genus of a nucleic acid sequence encoding a polypeptide having the activity of a first adenovirus serotype 52/55 kDa trans-acting protein and lacking the ability of a second adenovirus serotype 52/55 kDa trans-acting protein, and/or a genus of a vector system that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646

(1998). The skilled artisan cannot envision the detailed structure of a genus of the claimed nucleic acid sequence encoding a polypeptide having the activity of a first adenovirus serotype 52/55 kDa trans-acting protein and lacking the ability of a second adenovirus serotype 52/55 kDa trans-acting protein and/or vector systems that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 1-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) A vector system for selectively packaging a replication defective adenovirus nucleic acid sequence in an adenovirus capsid based on adenovirus serotype, comprising a first nucleic sequence comprising 5' and 3' adenovirus ITRs, an adenovirus serotype cis-acting packaging signal, a heterologous nucleic acid; and a helper virus comprising: 5' and 3' adenovirus ITRs, a second nucleic acid sequence encoding an adenovirus serotype cis-acting packaging sequence and a DNA sequence encoding a functional 52/55 kDa trans-acting protein; wherein the adenovirus serotype of the first nucleic acid sequence is different then adenovirus serotype in the second nucleic acid sequence; 2) A vector system for selectively packaging a replication defective adenovirus nucleic acid sequence in an adenovirus capsid based on adenovirus serotype, comprising a first nucleic sequence comprising 5' and 3' adenovirus ITRs, an adenovirus serotype cis-acting packaging signal sequence, a heterologous nucleic acid, and a DNA sequence encoding a mutated adenovirus serotype 52/55 kDa trans-

acting protein that is not functional; and a cell, which is genetically modified by transfecting the cell with a second nucleic acid sequence encoding a functional adenovirus serotype 52/55 kDa trans-acting protein, wherein the adenovirus serotype in the first nucleic acid sequence is different then adenovirus serotype in the second nucleic acid sequence and does not reasonably provide enablement for the rest of the disclosed embodiment; 3) The vector system of either 1 or 2, wherein the replication defective adenovirus comprises a defective E1 gene, E2 gene, E3 gene, E4 gene, E4 promoter, penton gene, fiber gene, hexon gene, or combination thereof and does not reasonably provide enablement for other claimed embodiments embraced by the breadth of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possession of a genus of a nucleic acid sequence encoding a polypeptide having the activity of a first adenovirus serotype 52/55 kDa trans-acting protein and lacking the activity of a second adenovirus serotype 52/55 kDa trans-acting protein), particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended, e.g. function in a vector system for selectively packaging replication defective adenovirus nucleic acid sequence in an adenovirus capsid.

Claims 1-39 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure, which is not enabling. A heterologous nucleic acid operably linked to a transcriptional sequence (e.g. promoter) is considered critical or essential to the practice of the invention, but not included

in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The claimed invention encompasses "a vector system comprising a heterologous nucleic acid sequence operably linked to a promoter" (pages 26-28). It appears from the specification that the active step for expressing a heterologous nucleic acid is by operably linking a transcriptional control sequence. In view of *In re Mayhew*, the claim is not enabled by the disclosure.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

With respect to claims 1-39, which encompass a vector system for selectively packaging a replication defective adenovirus nucleic acid sequence in an adenovirus capsid and a method of producing a replication defective encapsidated adenovirus gene transfer vector, the as-filed specification provides sufficient guidance for one skilled in the art to make 1) A vector system comprising a first nucleic sequence comprising: 5' and 3' adenovirus ITRs, an adenovirus serotype cis-acting packaging signal, a heterologous nucleic acid; a helper virus comprising: 5' and 3' adenovirus ITRs, a second nucleic acid sequence comprising an adenovirus serotype cis-acting packaging sequence and a DNA sequence encoding a functional 52/55 kDa trans-acting protein; 2) A vector system comprising a first nucleic sequence comprising 5'

and 3' adenovirus ITRs, an adenovirus serotype cis-acting packaging signal sequence, a heterologous nucleic acid, and a DNA sequence encoding a mutated 52/55 kDa trans-acting protein that is not functional (pm8001); and introducing pm8001 into a cell, which is genetically modified to express a functional 52/55 kDa trans-acting protein. One skilled in the art of producing adenovirus vectors, would understand that if an adenovirus vector comprises of only the two ITRs, an adenovirus packaging signal, a heterologous nucleic acid sequence, and a mutated 52/55 kDa protein that is not functional, it would require the presence of a helper virus or a cell line that provides the functions required for replication (E2 region), assembly (E1 region), and packaging (e.g. functional 52/55 kDa). The claims and the as-filed specification lack sufficient guidance for one skilled in the art to determine which genes are intended to be supplemented in trans to produce a vector system for selectively packaging a replication defective adenovirus nucleic acid sequence in an adenovirus capsid based on adenovirus serotype that can be used for its intended purpose (e.g. transfect cells). In view of the specification, one skilled in the art would determine that the disclosure intended to provide E1 and 52/55 kDa in trans (page 14, lines 4-13). Also, in view of the state of the art, one skilled in the art would be able to provide a E1 gene, a E2 gene, a E3 gene, a E4 gene, or adenoviral nucleic acid sequence needed to produce an adenoviral capsid in trans. However, in light of the as-filed specification and the state of the art for producing adenovirus vectors, the claims need to encompass which genes are/are not encompassed in the vector systems in order for the vector systems to

function as contemplated in the claimed embodiment (e.g. replication defective adenovirus vector).

Furthermore, with respect to claims 1 and 9, which encompass a vector system for selectively packaging a replication defective adenovirus nucleic acid sequence, wherein the replication defective adenovirus comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, penton gene, fiber gene, hexon gene, or combination thereof, one skilled in the art would determine in view of the as-filed specification and the prior art that the claims read on providing the complements to the defective or modified genes in a helper virus or a genetically modified cell expressing the genes. In light of this interpretation, the disclosure and prior art only provide sufficient guidance for the replication defective (non-functional) adenovirus early genes and the late genes [penton (L2); hexon (L3); fiber gene (L5)]. However, the disclosure does not provide sufficient guidance for one skilled in the art to modify (e.g. genes expressed at a higher or lower level than an endogenous adenovirus' early or late gene) any of the early or late genes contemplated claim 9. The state of the art for modifying adenovirus' genes as exemplified by Imperiale et al., Molecular biology of adenovirus gene therapy vectors. In. A. Cid-Arregui and A Garcia Carranca (eds): "Viral Vectors: Basic Science and Gene Therapy," Eaton, Natick, MA, pp. 119-128, Imperiale states:

> The ability to delete the E1 region is made possible by the existence of cell lines that provide these functions in trans (e.g. 293 cells). Until recently it has been difficult to construct viruses deleted for the E2 gene, as the toxicity of

> the E2 proteins has made the derivation of complementing cell lines tricky. The functional role of E3 gene in adenovirus vectors remains unclear, deletion of the E3, which is dispensable for viral growth in culture, does afford more room for transgene. A number of investigators have recently begun deleting various amounts of the E4 region from their vectors, with the hope that this will diminish replication and thereby permit longer persistence of the viral chromosome and, hence transgene expression in the cell by reducing the immune response against viral-encoded proteins. The results of the initial experiments have been mixed, however, and indicate that the exact effect of deleting E4 may depend on the target tissue. See pages 121-122.

In view of the state of art for producing helper viruses or cells that complement a defective or modified early or late gene and the unpredictability of using either E2 or E4 in trans, the as-filed specification fails to provide sufficient guidance for one skilled in the art to make modified adenovirus' gene(s) and try to complement the gene(s) by using a complementation system (e.g. helper virus). In addition, another concern that the disclosure fails to provide sufficient guidance, the two hurdles encompassing supplying the E2 protein in trans, which encompass: 1) that E2A should be expressed to very high levels and 2) that E2A protein is very toxic to cells. Thus, in light of the prior art and the as-filed specification and it would take one skilled in the art an undue amount of experimentation to reasonably correlate from using defective adenovirus genes to modifying adenovirus genes. Thus, the

disclosure is not enabled for modifying any adenovirus' early or late genes contemplated in claim 9.

In addition with respect to claims 36-39, which encompass a pharmaceutical composition comprising the vector system of claim 1 and a method of delivering a heterologous nucleic acid to a cell comprising transforming a cell using the pharmaceutical composition. The claims read on an in vivo and/or in vitro therapeutic method of gene therapy. The disclosure and prior art do not provide sufficient guidance for one skilled in the art to use the pharmaceutical composition in any therapeutic method of gene therapy. The state of the art for gene therapy as exemplified by Rubanyi (Molecular Aspect of Medicine, Vol. 22, 2001, pages 113-142) teaches that:

> The most promising areas for gene therapy today are hemophilias and cardiovascular diseases. This is based on the relative ease of access of blood vessels for gene therapy, and also because existing gene delivery technologies may be sufficient to achieve effective therapeutic benefits for some of these indication (transient expression in some but not all affected cells is required to achieve a therapeutic effect at a relatively low does of vector) (abstract). For other diseases (including cancer) further development in gene delivery vectors and gene expression systems will be required. It is important to note, that there will not be a universal vector and each clinical indication may require a specific set of technical hurdles to overcome. These will include modification of viral vectors, engineering of non-viral vectors by mimicking the beneficial

properties of viruses, cell-based gene delivery technologies, and development of innovative gene expression regulation systems (abstract).

Furthermore, Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method (Anderson, *Nature*, Vol. 392, pp. 25-30, April 1998).

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column

1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

The specification teaches a method for making replication defective adenovirus vector system (example 1). In addition, the as-filed specification lists several heterologous nucleic acids that could be used in a method of gene therapy. Also, the disclosure contemplated that the exact amount and concentration of virus and the amount of formulation in a given dose and the route of delivery can be determines by a clinician. Also, the disclosure contemplates transfecting germ or somatic cells in a mammal. The as-filed specification does not provide any working examples using the vector system for expressing any heterologous nucleic acid or what amount of heterologous nucleic acid is required to observed a therapeutic effect in a method of gene therapy. Furthermore, one skilled in the art of gene therapy would understand that adenovirus vectors rarely integrate into the host chromosome and is mostly suitable for transient expression. In addition with respect to route of administration (e.g. systemically, regionally, locally), "adenovirus vectors have been aimed at controlling local-regional diseases (e.g. cystic fibrosis or primary tumors)." See Imperial et al, Molecular biology of adenovirus gene therapy vectors. In. A. Cid-Arregui and A Garcia Carranca (eds.): "Viral Vectors: Basic Science and Gene Therapy," Eaton, Natick, MA, pp. 119-128. In these therapies the virus is delivered

directly to the affected tissue, and the spread of virus to surrounding non-diseased tissue is limited. This is an important issue, because it has been shown that systemic delivery of adenovirus can cause severe hepatotoxicity." See Imperiale, page 123. Imperiale further states:

> Obtaining persistence of a heterologous nucleic acid may be a more difficult task. Adenovirus vectors can stimulate an immune response in the host or the transgene itself could be immunogenic. Thus, clearance of cells transfected with the adenovirus vector can result in the loss of the therapeutic gene expression. While this might not be a problem in the treatment of diseases in which one wishes to kill the cell, such as cancer, it is a problem in other instances when long-term expression is desired. See page 124.

In view of the prior art, the specification fails to provide sufficient guidance for any method of gene therapy. In view of the In re Wands Factors, claims 36-39 are not enabled by the specification, which does not provide sufficient guidance for one skilled in the art to use the vector system for any therapeutic method of gene therapy. One skilled in the art of gene therapy would interpret that the breadth of the claim encompasses a therapeutic level of expressing a heterologous nucleic acid in a cell. However, in view of the breadth of the claims, the specification does not provide sufficient guidance for one skilled in the art to use the vector system described above for therapeutically treating any disease (e.g. hemophilia, cancer, etc.) or defects that require precise gene regulation (e.g. diabetes). In view of the doubts expressed above by Anderson, Rubanyi, and Verma, the specification and prior art at the time the

application was filed, the as-filed specification fails to provide sufficient guidance for one skilled in the art to reasonably extrapolate from making a replication defective adenovirus vector system to using the vector system in any method of gene therapy for delivering a heterologous nucleic acid to an in vitro cell and/or in vivo cell to therapeutically treat a genetic defect in any mammal. Furthermore, Rubanyi teaches:

> That some applications of gene therapy require no precise gene expression regulation because they involve proteins with large therapeutic windows (such as adenosine deaminase, CFTR, and coagulation factors VIII and IX). These applications, however, represent only a small part of the clinical potential for gene therapy. Most therapeutic proteins have limited therapeutic windows, both in terms of their level and their duration of action for effective protein delivery, control over the level and duration of gene expression (page 124).

Thus in view of the In Re Wands Factors, listed above, the quantity of experimentation required to determine the delivery route of a nucleic and what amount of nucleic is required to treat a genetic disorder that requires precise regulation of gene expression, the direction provided by the as-filed specification encompasses using gene therapy to treat any disease, the working examples encompass making a vector system, the state of the gene therapy was considered predictable when treating a genetic disorder that does not require precise gene expression, the relative skill of those in the art, and the breadth of the claims; the as-filed specification fails to provide sufficient guidance for how to correct any disease in any mammal. Furthermore, the as-filed specification lacks sufficient guidance for

the whole genus of pharmaceutical compositions, which would require an undue amount of experimentation for one skilled in the to determine which pharmaceutical composition displays a therapeutic effect in a mammal in view of the art of record displaying that a universal vector does not exist for use in treating any disease or disorder.

At best the disclosure is enabled for: 1) A vector system for selectively packaging a replication defective adenovirus nucleic acid sequence in an adenovirus capsid based on adenovirus serotype, comprising a first nucleic sequence comprising 5' and 3' adenovirus ITRs, an adenovirus serotype cis-acting packaging signal, a heterologous nucleic acid; and a helper virus comprising: 5' and 3' adenovirus ITRs, a second nucleic acid sequence comprising an adenovirus serotype cis-acting packaging sequence and a DNA sequence encoding a functional 52/55 kDa trans-acting protein; wherein the adenovirus serotype of the first nucleic acid sequence is different then adenovirus serotype in the second nucleic acid sequence; 2) A vector system for selectively packaging a replication defective adenovirus nucleic acid sequence in an adenovirus capsid based on adenovirus serotype, comprising a first nucleic sequence comprising 5' and 3' adenovirus ITRs, an adenovirus serotype cis-acting packaging signal sequence, a heterologous nucleic acid, and a DNA sequence encoding a mutated adenovirus serotype 52/55 kDa trans-acting protein that is not functional; and a cell, which is genetically modified by transfecting the cell with a second nucleic acid sequence encoding a functional adenovirus serotype 52/55 kDa trans-acting protein, wherein the adenovirus serotype in the first nucleic acid

sequence is different then adenovirus serotype in the second nucleic acid sequence and does not reasonably provide enablement for the rest of the disclosed embodiment; 3) The vector system of either 1 or 2, wherein the replication defective adenovirus comprises a defective E1 gene, E2 gene, E3 gene, E4 gene, E4 promoter, penton gene, fiber gene, hexon gene, or combination thereof.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable 1-3, listed above. Given that gene therapy wherein any carrier is employed to correct a disease or a medical condition in any mammal was unpredictable at the time the application was filed, and given the lack of sufficient guidance as to a gene therapy effect produced by the gene delivery vector cited in the claims or modifying adenovirus early or late gene(s), one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicants' disclosure and the unpredictability of gene therapy and modifying adenovirus early and late genes. Furthermore, the as-filed specification lacks sufficient guidance for the whole genus of pharmaceutical compositions, which would require an undue amount of experimentation for one skilled in the to determine which pharmaceutical composition would display a therapeutic effect in a mammal.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ms. Tracey Johnson whose telephone number is (703) 305-2982.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached at (703) 305-4051.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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November 19, 2001

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PRIMARY EXAMINER